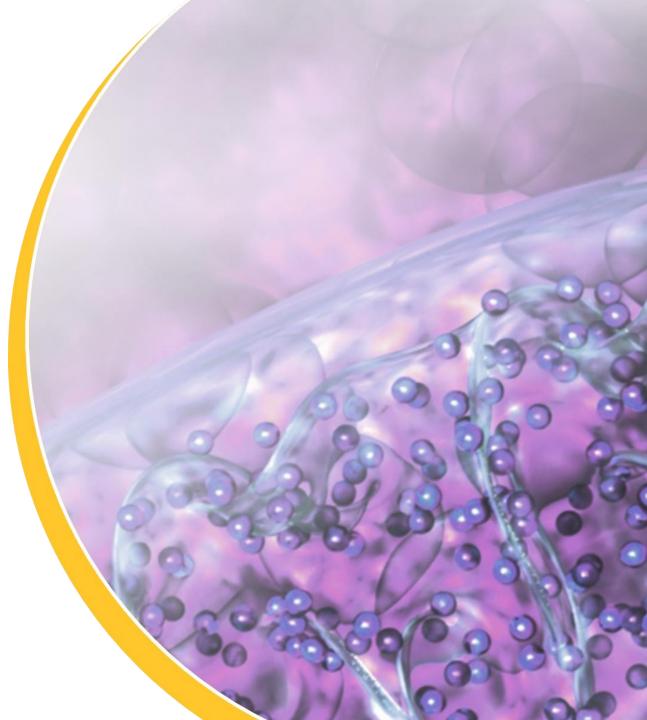
## **Epirium** Bio

## Novel Oral Therapy Significantly Improving Muscle Quality

Increasing Fast Twitch Muscle Strength & Function Addressing Pathologic Sarcopenia



## **Progress Highlights**





#### Ph 1 IND accepted - Enrollment Initiation Q4 '24

• Ph 1 data readout with Target Engagement Biomarker Q3 '25

#### **Characterized MF-300's Potential Human Benefit**

- Translation of MF-300 muscle benefit supported by Scholar Rock Ph 3 readout (SMA)
- Proteomic analysis identifies potentially relevant translational effects of MF-300
- Established PGE2-responsive human myocyte assay to test mechanistic hypotheses

#### **Correlated PD Biomarker to Target Dose Efficacy**

- PGE-MUM highest correlation with MF-300
- TD\* of 10mpk potential for circulatory biomarker tied to grip strength in aged population

#### Ph 2a Sarcopenia Study Plan: Transformational Value Opportunity

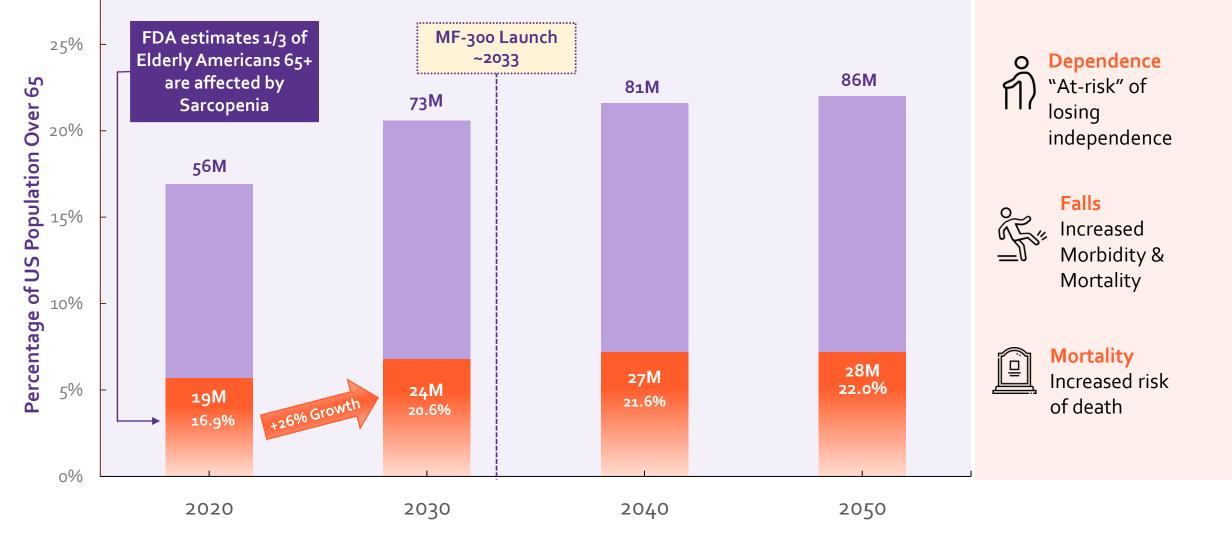
- Efficacy study: <u>PE</u>\* SPPB, QOL, Muscle Function & Disease Response Biomarker(s)
- Expecting first patient dosed Q4 '25 with data readout H2 '26
- Engaged with key stakeholders on registrational primary endpoints

TD= Target Dose PE = Primary Endpoint SPPB = Short Physical Performance Battery QOL= Quality of Life

## Sarcopenia: Large Unmet Medical Need with No FDA Approved Therapy

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#### Current U.S. Healthcare Sarcopenia Spending Estimated >\$40 Billion Annually



Source: Burns ER, J. Safety Res. 2016, U.S. Population est. 331M

## **Diminished Muscle Quality is a Root Cause of Sarcopenia**

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## Sarcopenia

- Severe loss of muscle strength and mass with aging
- Strength declines faster than muscle mass<sup>1</sup> due to Diminished muscle quality<sup>5</sup>
  - Existing muscle is weaker, contracts slower
  - Disproportionate loss of fast twitch muscle force
  - Progressive denervation of muscle
  - **Reduced regenerative potential** of muscle stem cells
- Age induced inflammation, Inflammaging, is a key driver of reduced muscle quality and muscle weakness<sup>4</sup>

<sup>1</sup>Cruz-Jentoft and Sayer, *Lancet* 2019 <sup>2</sup>Jubrias and Conley, *Fun. Neurobio. of Aging*, 2001 <sup>3</sup>Li et al., *Med Sci Sports & Exercise*, 2017 <sup>4</sup>Heinze-Milne et al., *Mech Aging Dev*, 2022 <sup>5</sup>Mohien et al., *eLife*, 2019

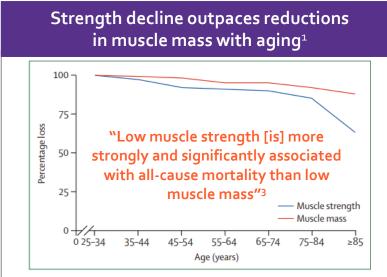


Figure 1: Percentage loss of muscle mass and muscle strength with age in men

#### Reduction in Muscle Quality Contributes >30% to Loss in Muscle Force in Elderly<sup>2</sup>



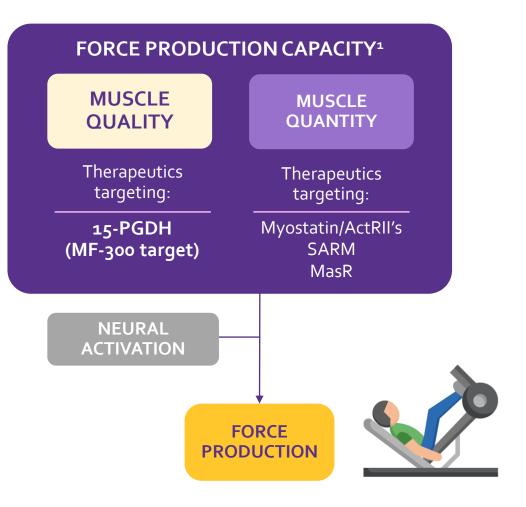
## Improving Muscle Quality in Sarcopenia: Differentiated Therapeutic Approach

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#### "Maintaining or gaining muscle mass does not prevent aging-associated declines in muscle strength"<sup>2</sup>

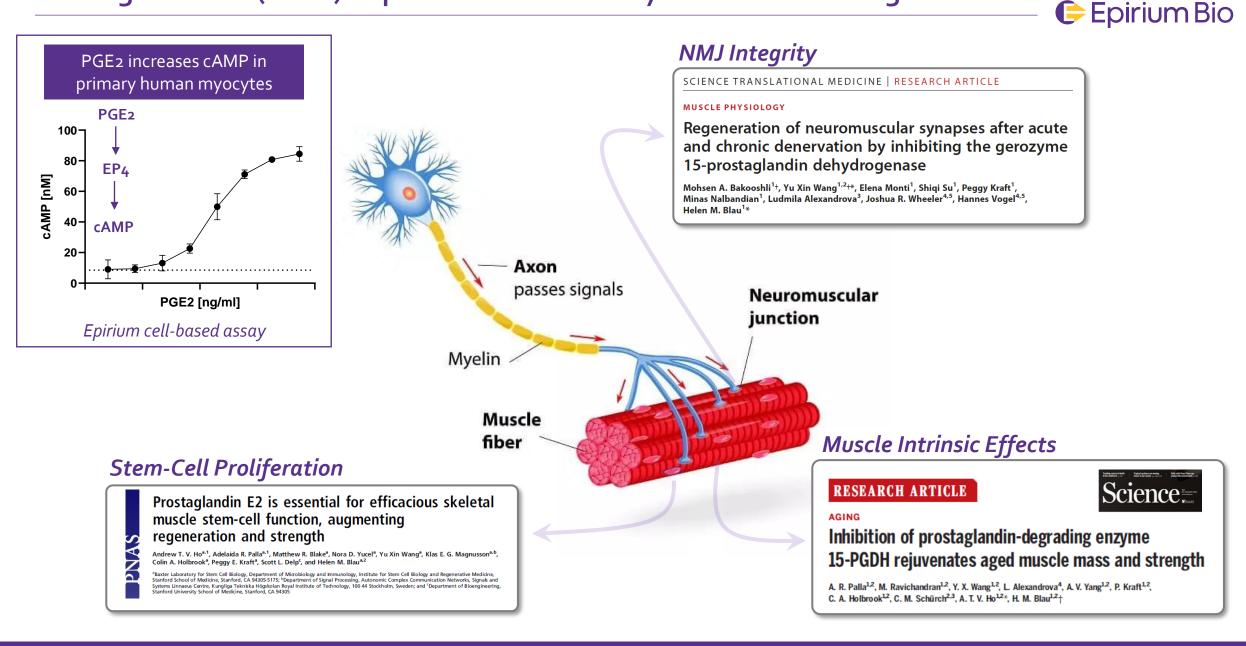
MF-300: First-in-Class Oral Therapy Improving Muscle Quality

- Broad applicability in aging
- Differentiated from adding muscle quantity
- Combination Tx potential



<sup>1</sup> Adapted from Jubrias and Conley, *Fun. Neurobio. of Aging*, 2001 <sup>2</sup> Goodpaster et al., *J Gerontology*, 2006

### Prostaglandin E2 (PGE2) Improves Muscle Quality and Function in Aged Mice

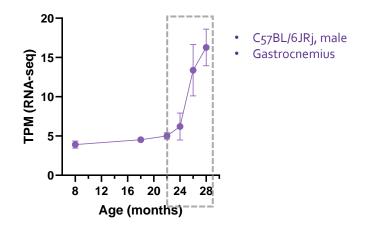


#### MF-300 Target: 15-PGDH Upregulated in Aging Muscle, Correlated w/ Strength Loss

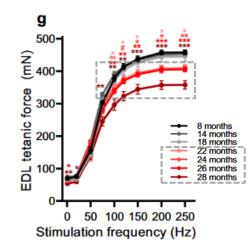


#### Aged Mice: 15-PGDH elevated

Muscle 15-PGDH gene expression (Hpgd) increases during aging<sup>1</sup>



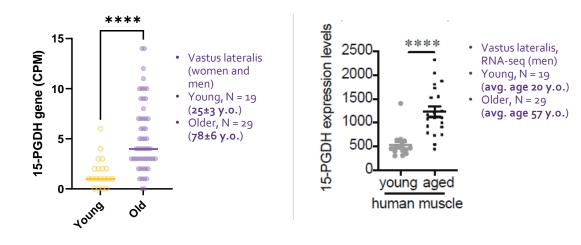
Muscle strength declines during window of elevated Hpgd<sup>2</sup>



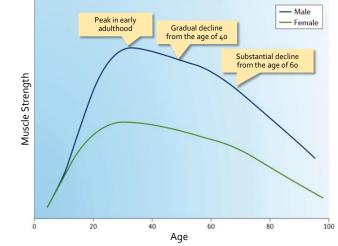
<sup>1</sup> https://sarcoatlas.scicore.unibas.ch/ GSE145480, <sup>2</sup> Borsch et al., Com Bio 2021

#### Elderly Humans: 15-PGDH elevated

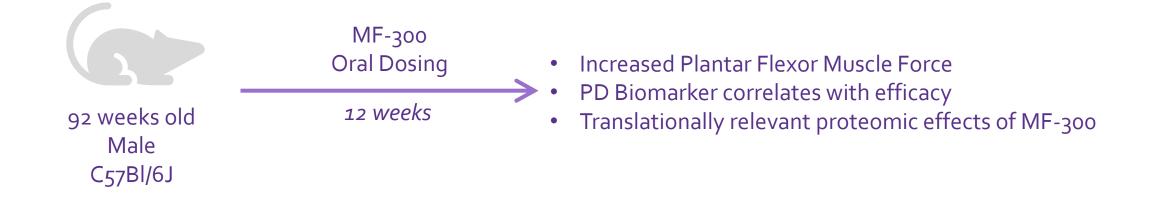
15-PGDH gene expression is elevated with aging in human muscle<sup>3,4</sup>



#### Grip strength, a predictor of sarcopenia risk, declines with age<sup>5</sup>



3 GEO167186, 4 Raue et al., J Appl Physiol 2012 (published in Palla et al., Science 2021), 5 Dennison et al., Nat Rev Rheum 2017



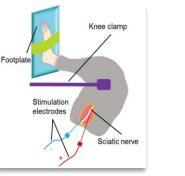
#### In vivo & ex vivo isometric force measured with a 305C muscle lever system (Aurora Scientific Inc., Aurora, CAN)

#### Reproducible results

- Defined stimulation parameters (amplitude, frequency, duration)
- Independent of fear driven motivation (e.g., grip, rotarod, wire hang)
- Measure several parameters of muscle function
  - Absolute force, contraction rate, relaxation rate, force/frequency response

In vivo Plantar Flexor Force Mixed fiber type

Ex vivo EDL Force Fast twitch





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## MF-300 Substantial Efficacy at Target Dose w/ Correlated PD Biomarker



#### MF-300: Repeated efficacy (muscle force) at Target dose across multiple studies in mice ≥90 weeks old

Study #	Mouse Strain, Age	Dosing, Duration	Endpoints	Status	Results
1	C57Bl/6J 90-92 weeks	Q2D, 12 weeks Vehicle & multiple dose groups	Muscle force, histology, proteomics, PD biomarker	Completed	<ul> <li>Target Dose max force &amp; increased contraction rate</li> <li>Target Dose greatest reduction in PD biomarker</li> </ul>
2	C57Bl/6J 90-92 weeks	Q2D, 12 weeks Vehicle & multiple dose groups	Muscle force <b>,</b> PD biomarker	Completed	<ul> <li>All doses stat. sign.</li> <li>Target Dose greatest reduction in PD biomarker</li> </ul>

#### Positive Proteomic Data From Study #1:

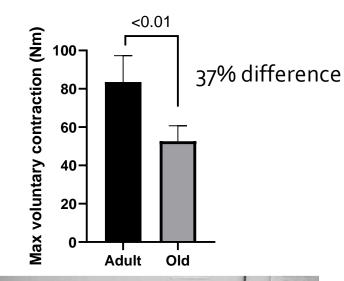
- ✓ Identified effects of MF-300 on the aged muscle proteome in mice
- ✓ Compared with human proteomic and genomic data, elucidated translational potential for MF-300's mechanism

#### Translational Model: Age Related Decline in Plantar Flexor (Calf Muscle) Force

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Male Old (N=11): 61-74 y.o.

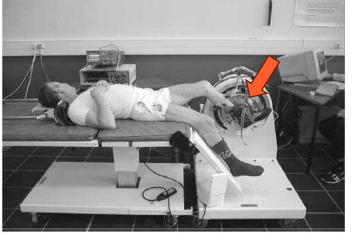


Adult (N=12): 19-24 y.o.

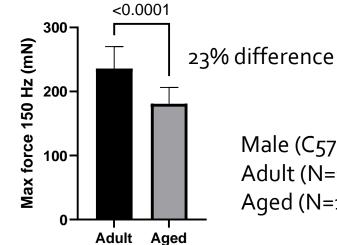
#### **Activities of Daily Living:**

- Pressing car pedals
- Extending body to reach
- Walking

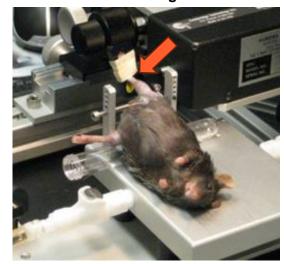
Graph generated from data published in Ochala et al., Exp Ger, 2004



Maximal voluntary contraction

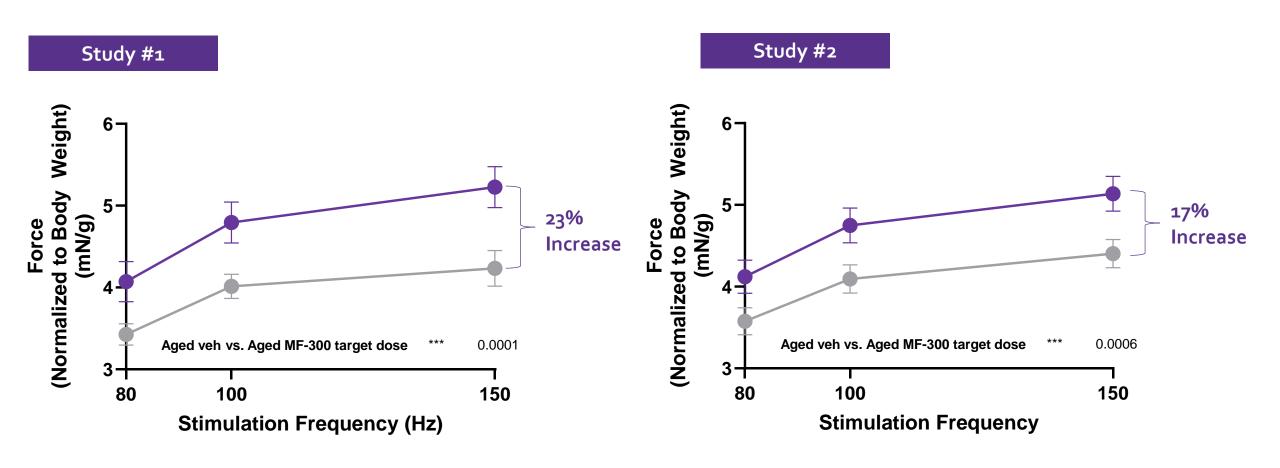


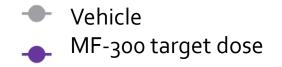
Male (C<sub>57</sub>Bl/6J) Adult (N=15): 12 m.o. Aged (N=18): 23 m.o.



Electrical nerve-evoked contraction

Mouse is anaesthetized Image from: https://aurorascientific.com/somet imes-two-is-better-than-one/

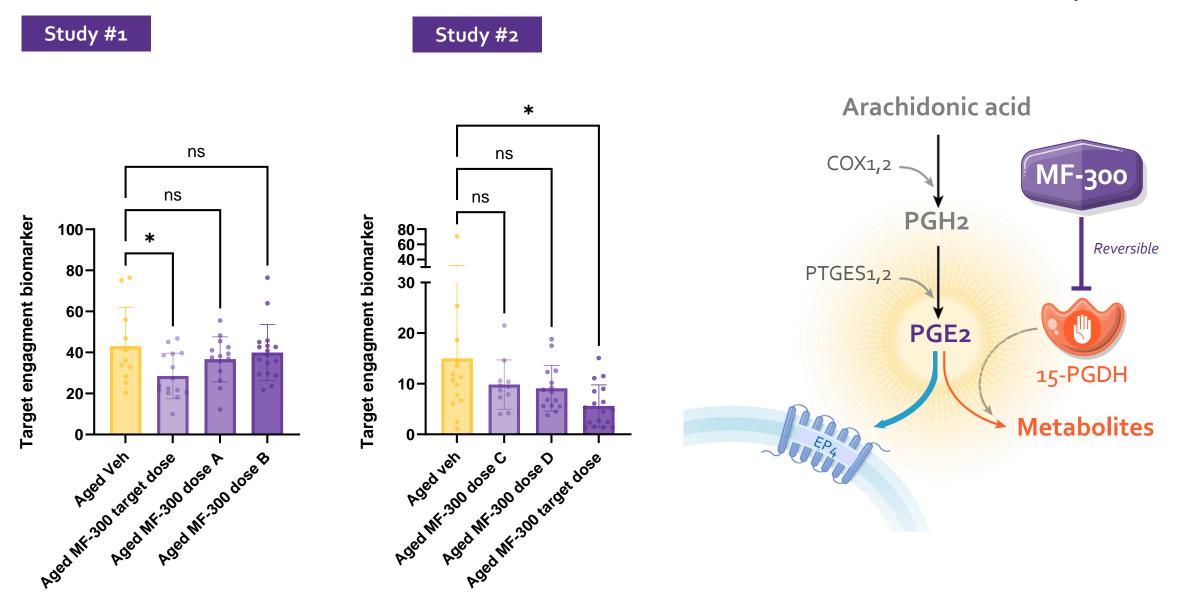




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### MF-300 Target Dose Significant Effect on Target Engagement Biomarker

— 🧲 Epirium Bio



## MF-300 Potential to Provide Substantial Benefit to Sarcopenia Patients

"Many older people highly value their independence with the desire outweighing other needs. Individuals go to great lengths to achieve independence...."

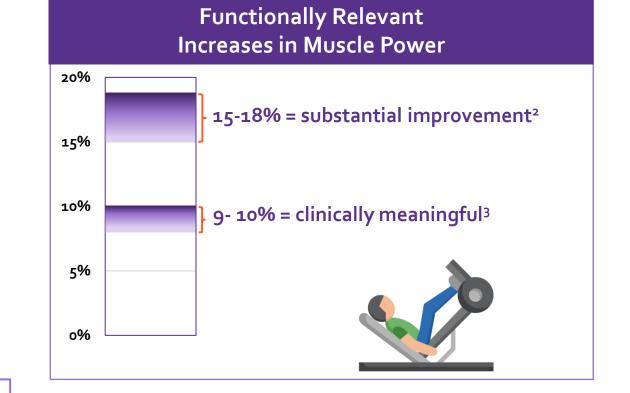
-Older Adults' Perspective of Independence Through Time: Results of a Longitudinal Interview Study<sup>1</sup>

"A significant number of sarcopenia patients are on the cusp of losing their independence. If MF-300's preclinical efficacy results are replicated in the clinic, MF-300 should provide a clinically substantial improvement, allowing sarcopenia patients to remain independent."

-Prof. Roger A. Fielding, Ph.D, Senior Scientist & Team Lead, Human Nutrition Research Center on Aging, Tufts University

Leg Power Dependent Key Functional ADLs:

- Climbing stairs, Getting out of a chair, Bathing Reflective Efficacy Endpoints (Leg Power):
- Stair Climb, Double Leg Press, Knee Extension, SPPB\*



#### Muscle Power = Muscle Force × Muscle Velocity

<sup>1</sup>Taylor et al, *The Genrontologist* , 2023 <sup>2</sup>Kirn et al., 2016; <sup>3</sup>Kirn et al., 2016

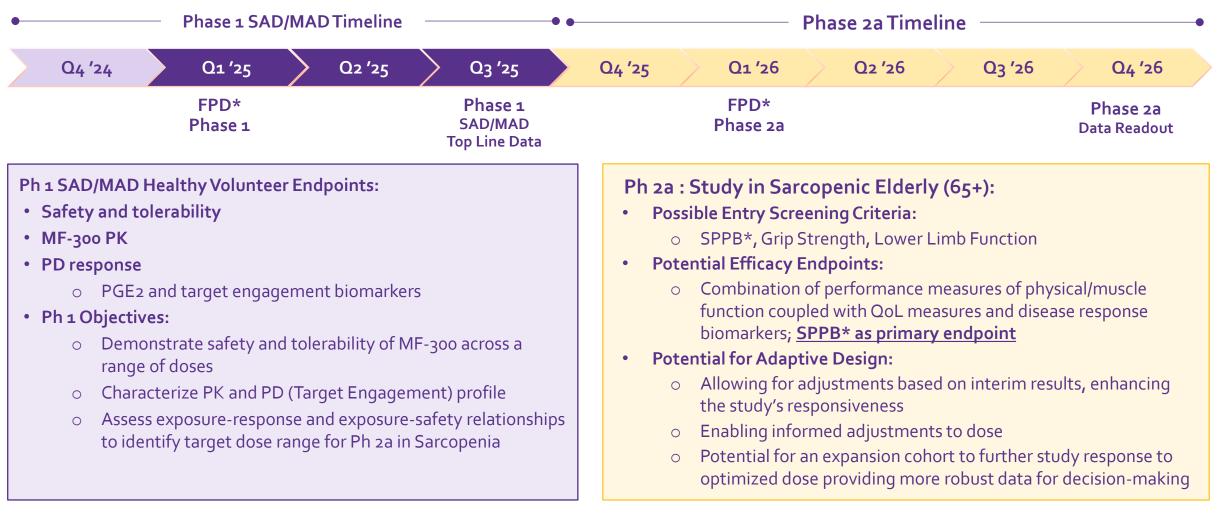
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\*Short Physical Performance Battery

## MF-300: On-track to Deliver Transformational Clinical Value

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#### MF-300 "First-in-Class" Oral Sarcopenia Tx: Ph 1 w/ TE\* biomarker Q3 '25, Ph 2a Efficacy Q4 '26

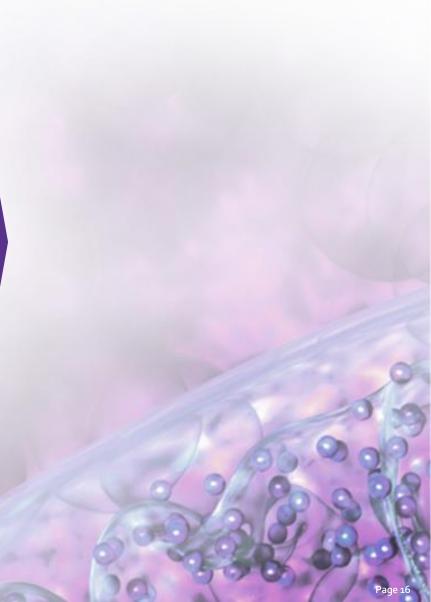


# Epirium Platform: Addressing High Value Indications with Unmet Medical Needs

DISEASE	Oral Compound	DISCOVERY PRECLINICAL PHASE 1	PHASE 2
Sarcopenia	MF-300	into a "first stage comp sarcopenia	pirium transforms -in-class" clinical pany targeting a large unmet need A approved therapies
Fibrosis	NCE1		
Neuromuscular	NCE2		

## **Supportive Material Information:**

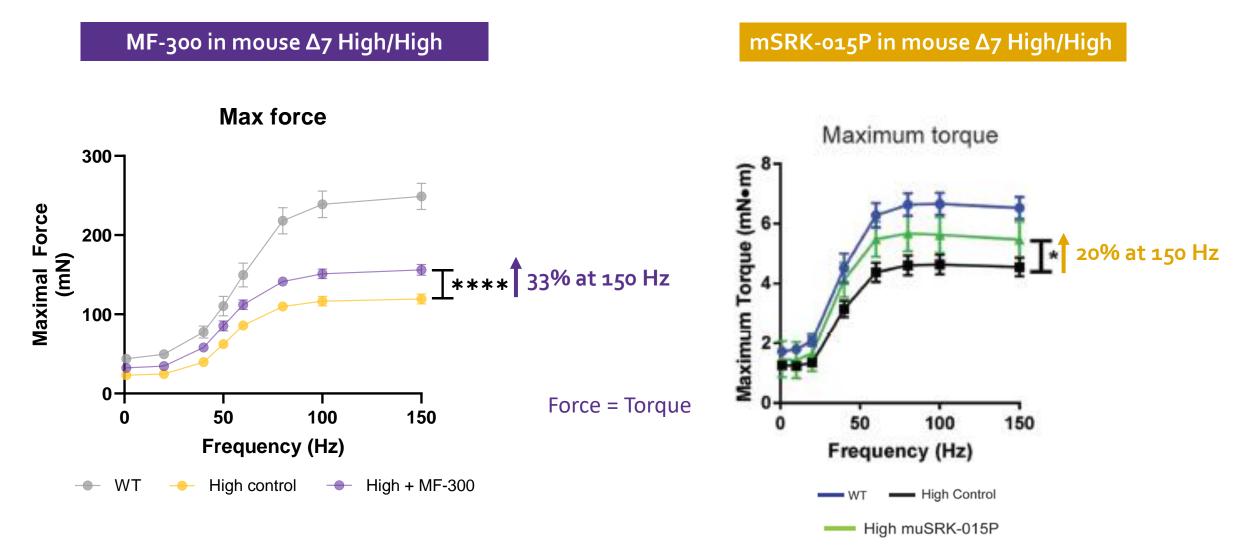
- Current Ownership
- MF-300 Comparison to murine Apitegromab in Delta 7 Mice





#### MF-300 Attractive Competitive Profile Compared to mSRK-015P in SMNA7 + SMN Upregulator

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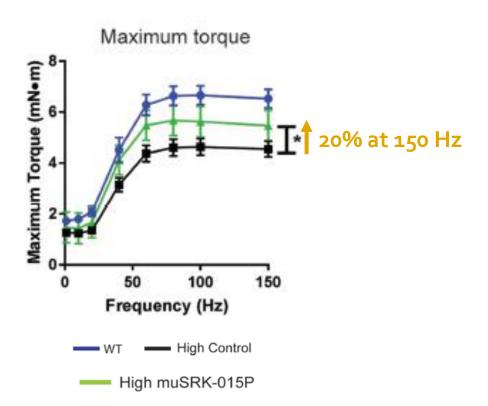
## **MYOLOGICA**

Long et al., Hum Mol Gen, 2019

#### Scholar Rock's Preclinical and Clinical Data Set Precedent for Translation of Efficacy

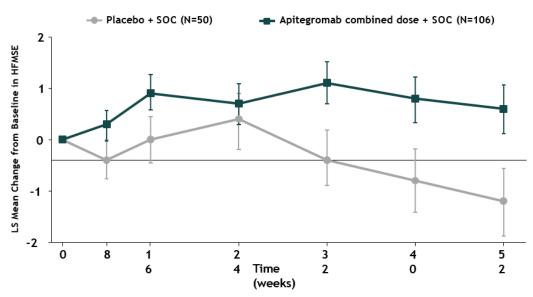
#### Demonstrates that a 20% increase in isometric plantar flexor force in mice translates to clinical benefit

mSRK-015P in mouse  $\Delta$ 7 High/High



#### Apitegromab in SMA + SOC (Ph 3 SAPPHIRE)

Least Squares Mean (+/- SE) Change from Baseline in HFMSE Total Score by Visit (MITT Set)



Change from Baseline in HFMSE Total Score

	Analysis	n	Results (vs Placebo, n=50)	Unadjusted <b>P</b> -value		
Primary Analysis	Apitegromab 10+20 mg/kg combined	106	1.8	0.0192*	Achieved Statistical Significance	
	Apitegromab 20 mg/kg	53	1.4	0.1149*		
	Apitegromab 10 mg/kg	53	2.2	0.0121**	🐝 Scholar <b>Rock</b>	

#### Long et al., Hum Mol Gen, 2016

**Epirium Bio**